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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/789,758 | 02/27/2004 | Joseph Cohen | B45187 C1 | 1891 |

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| EXAMINER | |
|---|---|
| MINNIFIELD, NITA M | |
| ART UNIT | PAPER NUMBER |
| 1645 | |

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/789,758 | COHEN ET AL. | |
| | Examiner | Art Unit | |
| | N. M. Minnifield | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 13-24 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 13-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 27 February 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/018,704.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892) 5pp.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/27/04 8 pp.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicants' preliminary amendment filed February 27, 2004 is acknowledged and has been entered. Claims 1-12 have been canceled. New claims 13-24 have been added. Claims 13-24 are pending in the instant application.

2. The disclosure is objected to because of the following informalities: At page 7, line 18, does Applicant intend "vaccine does" or "vaccine dose"? The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Appropriate correction is required.

***Sequence Requirements***

3. This application contains sequence disclosures (see page 6) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this office action. A complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with ***both*** these requirements in the time period set forth in this office action will be held non-responsive.

4. Claims 14, 15, 20, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 14 and 15 are indefinite because they contain the abbreviations "RTS", "RTS*" and "TRAP". Full terminology should be in each instance in the claims without the additional use of redundant abbreviations in parentheses or otherwise. Correction is required. Claims 14 and 15 are vague and indefinite in the recitation of "equivalent derivatives thereof"; what are the metes and bounds of equivalent derivative"? Claim 24 is vague and indefinite in the recitation of "suitable time"; how much time is "suitable time"? What are the metes and bounds of "suitable time"? What is the interval of time between the administrations of the two components to the patient that is considered suitable? Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. With regard to claim 23, what are the components of the composition such that one of skill in the art would know that the method steps had achieved the claimed composition? The method also needs a final product step. With regard to claim 24, to whom is this composition being administered? The claim needs to recite "administering to a patient an effective...". Claim 20 is vague and indefinite in the recitations of "WD1001..."; these oligonucleotides should also recite their respective sequence identification number (i.e. SEQ ID NO:).

5. Claims 13, 21, 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of amelioration of

plasmodium infection in a patient comprising administering a composition comprising a malaria antigen and CpG to the patient, does not reasonably provide enablement for methods for the prevention of plasmodium infection in a patient comprising administering a composition comprising a malaria antigen and CpG to the patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to methods for the prevention of plasmodium infection in a patient comprising administering a composition comprising a malaria antigen and CpG to the patient. The specification contemplates that the patient can be a human (see the abstract). The malaria antigen is not specifically defined in the specification. The specification teaches that immunization with RTS,S (a hybrid of CSP from *P. falciparum* and protein from hepatitis B virus) in combination with CpG or CpG/alum induces HBsAg-specific CTL in mice (see p. 11). The specification also teaches that immunization with RTS,S in combination with CpG induces immune responses in non-human primates (rhesus monkeys). After two immunizations CpG alone induces low level HBsAg-specific antibodies, while CpG combined with alum induces high titer antibodies as well as vigorous lymphoproliferative and IFN-gamma responses (see p. 14). However, the specification does not teach that the composition as set forth in the claims, a composition comprising a malaria antigen and CpG, has prevented plasmodium infection in a patient, human or non-human primate. The specification is not enabled for a composition that prevents plasmodium infection; the specification does not set forth active immunization of a patient (non-human primate, animal or human) using the claimed composition, followed by a challenge.

The state of the art indicates that at present there are no vaccines that protect against malaria. Arevalo-Herrera et al indicates that because of the complexity of the parasite's life cycle the development of a universal, effective and long lasting vaccine is difficult (p. 444). Arevalo-Herrera et al states that since the use of whole malaria parasites as vaccines is not feasible, parasite sub-unit vaccines are being envisaged either making use of recombinant technology, peptide synthesis or naked DNA injection. Even though it is accepted that malaria vaccines need to simultaneously target the different parasite developmental stages, most vaccine trials concentrate on individual parasite targets, especially from *P. falciparum*. The of a multi-stage and multi-species vaccine is expected to be advantageous because of simultaneous priming of synergistic immune mechanisms targeting the main parasite species circulating in a given region. (p. 444, col. 2) Arevalo-Herrera et al indicates that even though most efforts towards vaccine development have been focused on *P. falciparum*, development of a worldwide efficient malaria vaccine will require the inclusion of components from two prevalent malaria species, *P. falciparum* and *P. vivax* at least (p. 444, col. 2). Bouharoun-Tayoun et al 2004 states that the study of parasite antigens targeted by ADCI effector antibodies has led to the characterization of MSP-3, a 48 kDa protein present on the surface of the *P. falciparum* merozoite. Cytophilic antibody response against MSP-3 is highly correlated with protective immunity. MSP-3 is currently used as a candidate malaria vaccine in clinical trials (p. 2, col. 1). The art indicates that it is a vaccine candidate but to date no vaccine against malaria using MSP-3, the whole protein or portions of the protein, has been disclosed.

Further, the art teaches problems with other proteins from Plasmodium as vaccine components. Kurtis et al 2001 states that a vaccine is urgently needed to

stem the global resurgence of *P. falciparum* malaria; LSA-1 is one of a few proteins known to be expressed by liver-stage parasites, holds particular promise as a vaccine (abstract). Kurtis et al 2001 states that despite "important advances, such as the circumsporozoite protein (CSP)-based vaccine called RTS,S, the goal of a safe and broadly effective malaria vaccine remains unfulfilled. The parasite's complex life-cycle offers several targets for intervention in the human host and the mosquito vector and vaccines against sporozoite, intrahepatic, blood and sexual stages of the parasite are currently in development." (p. 219, col. 1). As of 2001, there is no effective vaccine that comprises the LSA either alone or in combination with other malaria proteins. Further, because LSA is a liver specific antigen, investigation of its immunological significance is restricted to human studies because no homologue in mouse or non-human primate malarias has been identified (p. 219, col. 1). Others such as Taylor-Robinson et al 2001 have also indicated that LSA-1 may be a good candidate for a vaccine, but no vaccine has been produced that has been shown to be effective (see also Moorthy et al 2004; Ballou et al 2004; Joshi et al 2000; Kurtis et al 1999; Cox 1992; Ntumngia et al 2004; Stowers et al 2001). Shi et al, 1999 indicate that a multicomponent, multistage malaria vaccine can induce immune responses that inhibit parasite development at multiple stages. The rationale and approach used in the development of a multicomponent *P. falciparum* vaccine will be useful in the development of a multispecies human malaria vaccine and vaccines against other infectious diseases (see abstract). "Although studies of immunogenicity and the results of *in vitro* protection experiments have been promising for many of the single stage-specific vaccine candidate antigens, the test of *in vivo* protection has not always been satisfactory. There is consensus, however, that a highly effective

malaria vaccine would require a combination of key antigens and/or epitopes from different stages of the life cycle and that induction of both humoral and cellular immunity is required for optimal efficacy. Such a multicomponent malaria vaccine would also circumvent the problems associated with host genetic restriction and antigenic variability in the case of single antigen-based vaccines." (Shi et al, 1999, p. 1615, paragraph bridging cols. 1-2). Shi et al 1999 also indicates that multiple protective immune responses against multiple antigens from different stages will be needed to protect against malaria (p. 1618, col. 2). "Although a single-antigen and/or stage-specific vaccine could provide protection against infections, there are several reasons to advocate a multivalent, multistage malaria vaccine. A major concern with a single antigen-based vaccine is that an antigenic variant population of the parasite not recognized by the vaccine will cause infection (with heterologous parasites) and cause disease." (see p. 1618-1619).

In view of the fact that the specification does not set forth any enablement with regard to direction or guidance and the absence of working examples for the claimed composition and method for prevention of plasmodium infection in a patient, and the fact that the state of the art teaches that there are no single antigen (MSP-3b peptide or MSP-3c peptide or MSP-3d peptide or combinations of these peptide) or stage specific vaccines against malaria and the unpredictability and difficulty in obtaining an effective composition comprising a malaria antigen to prevent plasmodium infection in a patient, there would be undue experimentation necessary for a person of skill in the art to practice the claimed invention.

The prior references are cited to show that even after the filing date of the instant application, the development of a vaccine against malaria using any antigen or method of preventing plasmodium infection is a patient has not been achieved.

The state of the art at the time of filing is what is considered with regard to enablement. The amount of direction or guidance presented in the specification and the absence of working examples is a hindrance to practicing the claimed invention. One skilled in the art would not accept on its face in view of the lack of examples given in the specification as being representative of the successful composition to prevent plasmodium infection in a patient in view of the lack of guidance in the specification and the known unpredictability associated with malaria vaccines and methods of prevention.

It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed *in vivo* method.

Further, the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed

invention pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a)) In view of all of the above, the pending specification does not enable the claimed invention of methods for the prevention of a plasmodium infection in a patient.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 13, 17-21, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Caulfield WO 98/52962.

The claims are directed to a composition comprising a malaria antigen and an immunostimulatory CpG oligonucleotide, as well as methods of producing the composition and using said composition in a method for prevention or amelioration of plasmodium infection in a patient.

Caulfield discloses a composition comprising a oligonucleotide adjuvant and antigen and methods of vaccination using the composition (abstract; p. 6; p. 11; claims). Caulfield discloses an oligonucleotide having the CpG motif (p. 5). Caulfield discloses that the antigen can be antigens from *Plasmodium* (i.e. malarial antigens) (see p. 7). Caulfield discloses that the antigen and adjuvant are administered closely in time, e.g. the adjuvant is administered within from about one minute to within about one day before or after the antigen is administered (p. 8).

Jones et al discloses compositions comprising malarial antigens and synthetic oligonucleotides containing CpG motif as adjuvant (abstract). Jones et al discloses that these oligonucleotides are based on immunostimulatory bacterial DNA sequences (abstract). Jones et al discloses methods of preparing the composition as well as methods of administering the composition to a animal (materials and methods, p. 3066-67).

The prior art anticipates the claimed invention. The products disclosed in the prior art reference appears to be the same or obvious or analogous variants of the products claimed by Applicants because they appear to possess the same or similar elements or functional characteristics. The prior art is believed to inherently possess properties, which anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicants' products and methods and the products and methods of the prior art, the burden is on applicant to show a novel or unobvious differences between the claimed products and methods and the products and methods of the prior art (i.e., that the products and methods of the prior art does not possess the same material structural and functional characteristics of the claimed products and methods). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. Claims 13-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Friede et al 6558670.

Friede et al discloses a composition comprising a immunostimulatory oligonucleotides (i.e. CpG), saponin and an antigen (abstract; col. 9; claims). Friede et al discloses that the antigen can be from *P. falciparum* (i.e. malarial antigen) and that the composition may comprise combinations of more than one immunostimulatory oligonucleotide (cols. 5-6). Friede et al discloses that the vaccines "of the present invention further comprise antigens from parasites that cause Malaria. For example, preferred antigens from *Plasmodia falciparum* include RTS,S and TRAP." (see col. 7). The prior art also sets forth methods of preparing the composition as well as methods of administering the composition to prevent or ameliorate *Plasmodium* infections in a patient (cols. 3, 8, 10).

The prior art anticipates the claimed invention. The products disclosed in the prior art reference appears to be the same or obvious or analogous variants of the products claimed by Applicants because they appear to possess the same or

similar elements or functional characteristics. The prior art is believed to inherently possess properties, which anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicants' products and methods and the products and methods of the prior art, the burden is on applicant to show a novel or unobvious differences between the claimed products and methods and the products and methods of the prior art (i.e., that the products and methods of the prior art does not possess the same material structural and functional characteristics of the claimed products and methods). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

10. Claims 13 and 16-23 are rejected under 35 U.S.C. 102(e) as being anticipated by Davis et al 6406705, Krieg et al 6207646, or Raz et al 6589940.

Davis et al discloses compositions comprising synergistic adjuvants (CpG and non-nucleic acid adjuvant) and antigen (abstract). The antigen can be a parasite antigen (i.e. malarial antigen) (see col. 2; col. 16). The non-nucleic acid adjuvant can be saponins or MPL (col. 4; col. 14). Davis et al discloses that the oligonucleotide size can be 8 to 100 nucleotides, preferably 8 to 40 nucleotides (col. 4; col. 11). The prior art discloses methods of preparing the composition and administering the composition.

Krieg et al discloses compositions comprising a CpG adjuvant and antigen (abstract). The antigen can be a parasite antigen (i.e. malarial antigen) (see col. 11; col. 16). The non-nucleic acid adjuvant can be conventional adjuvants such as alum (col. 33). Krieg et al discloses that the oligonucleotide size can be 8 to 40 nucleotides (col. 6; col. 11). The prior art discloses methods of preparing the

composition and administering the composition (claims; col. 34). Krieg et al discloses that the compositions can be used to treat, prevent, or ameliorate and immune system deficiency (i.e. parasitic infection) (see col. 6).

Raz et al discloses compositions comprising immunostimulatory oligonucleotides, CpG, and antigens (abstract). The antigen can be a parasite antigen (i.e. malarial antigen) (see col. 5; col. 16). The composition can comprise additional adjuvants (col. 6; col. 13-16). Raz et al discloses that the oligonucleotide size can be 6 to more than 20 nucleotides (col. 10). The prior art discloses methods of preparing the composition and administering the composition (col. 12).

The prior art anticipates the claimed invention. The products disclosed in the prior art reference appears to be the same or obvious or analogous variants of the products claimed by Applicants because they appear to possess the same or similar elements or functional characteristics. The prior art is believed to inherently possess properties, which anticipates the claimed invention.

Since the Office does not have the facilities for examining and comparing applicants' products and methods and the products and methods of the prior art, the burden is on applicant to show a novel or unobvious differences between the claimed products and methods and the products and methods of the prior art (i.e., that the products and methods of the prior art does not possess the same material structural and functional characteristics of the claimed products and methods). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

11. No claims are allowed.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM

September 30, 2005